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Year: 2021

Version: Published version

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Manuscript received: February 3, 2021; Revised manuscript received: March 5, 2021; Version of record online: ■ ■ ■ ■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100162

COMMUNICATIONS
DOI: 10.1002/adsc.202100162

Abstract: By visible-light photoredox catalysis with copper complexes, sulfoximidoyl chlorides add to terminal aryl alkynes to give the corresponding (E)-β-chlorovinyl sulfoximines with exclusive regio- and stereoselectivities in high yields. Two representative products have been characterized by X-ray crystal structure analysis. Radicals appear to be decisive intermediates. As demonstrated by two subsequent reactions, the products can be derivatized.

Keywords: alkyne addition; copper catalysis; difunctionalization; vinyl sulfoximine; visible-light photoredox catalysis

Difunctionalizations of alkynes leading to olefins have attracted much attention. [1] To be of synthetic value, reactions with unsymmetric substrates require high regio- and stereoselectivities. For achieving this goal, various activation modes involving metal catalysts, visible light, or electrochemistry, for example, have been investigated. [2] Mechanistically, most additions can be characterized by radical and nucleophilic pathways. For synthetic purposes, alkyn difunctionalizations with sulfur-based reagents proved particularly useful. In this context, chlorosulfonylations of alkynes (Scheme 1, top) have continuously been studied in the last decades. Very early work stems from Amiel, who described the application of both copper(I) and copper (II) salts in catalyzed additions of sulfonyl chlorides 1 to alkynes 2. [3] As a result, he obtained trans- and cis-addition products 3 in variable ratios. For the diastereoselectivity the solvent and the presence of chloride ions played an important role. Free sulfonyl radicals A were suggested to dominate the reaction path. By modifying the copper catalyst, Liang and co-workers achieved exclusive cis additions to give (Z)-β-chlorovinyl sulfones from terminal alkynes. [4,5] Also iron salts have been used for promoting such additions. [6] More recently, sulfonyl chloride additions to alkynes have been initiated by visible light photoredox catalysis. [7,8] An example is Han’s work, who observed highly stereoselective trans additions affording (E)-β-chlorovinyl sulfones by using an iridium catalyst/blue light combination for the activation. [8a]

In each of the aforementioned examples, sulfonyl radicals A have been proposed to be key intermediates. In contrast to this very well-established field, nothing can be known about the reaction behaviour of the structurally closely related sulfoximidoyl radicals B (Scheme 1, bottom). Undoubtedly, analogous addition reactions of sulfoximidoyl chlorides 4 to alkynes 2 are of interest as they should lead to specifically substituted vinyl sulfoximines 5 with numerous potential applications in organic synthesis. [9,10] Realizing this opportunity, we decided to investigate such transformations and report the first results here.

In light of the very impressive advances in visible-light photoredox catalysis with copper complexes, [11] we decided to focus on studying the potential of such systems. For an initial screening and optimization of the reaction conditions, N-tosyl-protected sulfoximidoyl chloride 4a and phenylacetylene (2a) were

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selected as starting materials. To our delight, both compounds reacted when irradiated in THF for 8 h at room temperature with blue LED light in the presence of copper(II) chloride (10 mol%) and dtbpy (dtbpy = 4,4’-di-tert-butyl-2,2’-bipyridine, 20 mol%) providing addition product 5a in 10% yield (Table 1, entry 1).

Encouraged by this result, several solvents were tested (Table 1, entries 1–7), and among THF, DMF, toluene, EtOH, CCl₄, 1,4-dioxane, and DCM, the latter proved optimal leading to 5a in 52% yield (Table 1, entry 7). Substituting CuCl₂ by NiCl₂ and PdCl₂ proved ineffective (Table 1, entries 8 and 9). Other copper salts led to product formation, but generally, the yield of 5a was lower than with CuCl₂ (Table 1, entries 10–14). The only exception was copper(I) chloride which gave 5a in 65% yield (Table 1, entry 11). Changing the ligand from dtbpy to Xphos (Xphos = 2-dicyclohexylphosphino-2’,4’,6’-trisopropylbiphenyl) inhibited the catalysis with CuCl₂ (Table 1, entry 15). In contrast, combination of CuCl with 1,10-phen (1,10-phenanthroline) and dmbp (6,6-di-methyl-2,2-bipyridine) gave better results with yield for 5a of 75% and 80%, respectively (Table 1, entries 16 and 17). Providing an inert atmosphere by performing the catalysis with CuCl/dmbp under argon had almost no effect leading to 5a in 78% yield (Table 1, entry 18). Thus, the optimal conditions established for the addition of 4a to 2a to give 5a (in 80% yield) involved the use of a combination of 10 mol% of copper(I) chloride and 20 mol% of dmbp to be applied in DCM under irradiation with blue LED light for 8 h at room temperature (Table 1, entry 17).[12]

Next, the substrate scope was evaluated. Scheme 2 shows the results. First, the alkyne 2a was varied and reactions with sulfoximidoyl chloride 4a were studied. In general, all products 5a–m were obtained in good to high yields ranging from 49–87%. The reactions were highly regio- and diastereoselective providing single isolated products. Substrates with electron-donating substituents on the arene gave slightly higher yields of the corresponding products than those with electron-withdrawing groups. For example, while alkyne 4c with a 4-methoxy substituent gave 5c in 85% yield, the analogous compound bearing a 4-formyl group led to 5g in only 49% yield. The position of the substituent was of minor importance as revealed by the results for the three fluoro-substituted products, which were obtained in yields of 71% (5e, para), 82% (5j, meta), and 87% (5k, ortho), respectively. Also, 2-thiophenyl and 2-naphthyl-containing alkynes 2l and 2m reacted well with 4a affording 5l and 5m in yields of 62% and 71%. Performing the addition of 4a to 2a on a 2 mmol scale gave 5a in 64% yield.[13]

The molecular structures of two representative products in the series, 5b and 5f, were determined by X-ray crystal structure analysis,[14] and both showed the formation of trans addition products (Scheme 2). The regioselectivities corresponded to sulfur additions at the terminal positions of the alkynes.

Subsequently, reactions between phenylacetylene (2a) and a number of sulfoximidoyl chlorides including those with S-aryl and S-alkyl groups leading to
products 5n–x were studied. Those results are shown in Scheme 2 too.

In the series, electronic effects induced by S-aryl substituents appeared to be of minor importance, and the product yields were mainly dominated by steric factors. Thus, with the exception of S-3-fluorophenyl-containing product 5s, which was isolated in 91% yield, the average results for substrates with para-substituted S-aryl groups (5n–p) were generally better than those for products with ortho-substituted S-aryls (5t and 5u). S-2-Naphthyl-containing addition product 5v was isolated in 73% yield. Also S-alkyl sulfoximidoyl chlorides (specifically 4w and 4x) could be applied, and the corresponding products 5w and 5x were obtained in 68% and 74%, respectively.

To gain insight into the reaction details and to verify potential reaction pathways, several control experiments were performed. Again, phenylacetylene (2a) and sulfoximidoyl chloride 4a served as representative substrates. The observations are summarized in Scheme 3.

First, under standard conditions, the presence of CuCl and ligand, as well as the LED irradiation were critical. As shown in individual experiments any change along these lines led to a significant drop in yield of 5a from the previously determined 80% to only a trace amount. However, that was different, when the reaction was performed at 80 °C instead of the commonly applied ambient temperature. Now, 5a was obtained in 68% yield in the dark. Hence, under standard conditions visible light was essential, but the addition of 4a to 2a could also be initiated by raising the reaction temperature. The presence of both 2.0 equivs. of either TEMPO or BHT inhibited the product formation suggesting a relevance of radicals. Finally, performing the catalysis under standard conditions and offering 2.0 equivs. of thiocyanate (SCN⁻) or fluoride (F⁻) ions (in form of their K⁺ salts) as nucleophiles did not result in the formation of the corresponding addition products 6a or 6b (as analyzed by TLC and ESI MS). This result indicated that cationic intermediates were unlikely.

Based on these observations and considering the results from other studies, in particular those related to additions of sulfonyl radicals to alkynes[3–8] and visible light photocatalysis with copper complexes,[11] the mechanism depicted in Scheme 4 can be proposed.

The product formation is initiated by generation of sulfoximidoyl radical B from sulfoximidoyl chloride 4 upon irradiation with visible light in the presence of the copper complex. In this process, which can also be
promoted (in the dark) by raising the temperature, the original ligand-bound copper(I) complex is oxidized to give the corresponding copper dichloride complex. Addition of radical B to the alkyne is regioselective and leads to a new radical species C, which can subsequently follow two pathways. On path a, C interacts with the previously generated ligand-bound copper(II) complex to give a copper(III) intermediate D, which upon reductive elimination provides product 5. Presumably, the pronounced stereoselectivity of the reaction is determined in the formation of intermediate D, where the sterically demanding sulfoximidoyl substituent is trans to the large copper(III) group. Retention of configuration in the reductive coupling step would then lead to the observed E-isomer of 5. TEMPO or BHT would interfere with any of the involved radicals thereby inhibiting the product formation. The alternative route to 5 (path b) involves radical C too, this time, however, C is oxidized by CuCl₂·dmbp to give cation E. The resulting copper(I) complex can re-enter the catalytic cyclic, and cation E reacts with chloride ions to afford addition product 5. Although path b cannot rigorously be excluded, we regard it less likely based on the results of the trapping experiments with other nucleophiles reported in Scheme 3, where neither 6a nor 6b were detected. Furthermore, the high stereoselectivity in the formation of E would be difficult to rationalize.\[15,16\]

With the goal to demonstrate the synthetic applicability of products 5 by subsequent functional group modifications, two structural changes were investigated (Scheme 5). In both cases, 5a served as representative starting material. Applying Suzuki-type cross-coupling conditions with phenyl boronic acid as reagent and a palladium(II)/Xphos combination led to arylated product 7 in 81% yield.\[17\] The formation of thioether 8 was achieved by treatment of 5a with a mixture of thiophenol and sodium methoxide in methanol, which provided 8 in 85% yield.

Scheme 4. Plausible mechanism for the product formation.

Scheme 5. Product modifications.

In summary, we developed a visible-light photoredox process with copper complexes as catalysts leading to vinylic sulfoximine derivatives by highly regio- and stereoselective additions of sulfoximidoyl chlorides to terminal arylalkynes. The molecular structures of two representative products were determined by single crystal X-ray diffraction analysis. A wide range of functional groups is tolerated, and the yields are good. Mechanistic studies suggest the involvement of radicals as key intermediates. By two subsequent functional group modifications, potential synthetic applications have been exemplified.

Experimental Section

General procedure for preparation of vinyl sulfoximines 5 as exemplified for the synthesis of 5a. A mixture of 4a (65.8 mg, 0.2 mmol), 2a (40.8 mg, 0.4 mmol), CuCl (2.0 mg, 0.02 mmol), dmbp (7.4 mg, 0.04 mmol), and DCM (1.0 mL) in a sealed 5 mL glass vial was irradiated with blue LED light at room temperature for 8 hours. Then, the reaction mixture was concentrated in vacuo. Finally, the resulting product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 6/1–4/1) to give 69.0 mg (80% yield) of product 5a as a white solid.

Acknowledgements

P.S., Y.T., D.Z., and C.W. are grateful to the China Scholarship Council for predoctoral stipends. K.R. appreciates the support by the Alexander von Humboldt Foundation (AvH research award). Open access funding enabled and organized by Projekt DEAL.

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[13] Attempts to 4a under standard conditions onto 1-phenyl propyne and 1,2-diphenylethylene representing internal alkynes remained unsuccessful.


[16] Generating the sulfoximidoyl radical from sulfoximidoyl chloride 4a by metal-free methods and to add it to 2a proved possible, but the outcome remained unsatisfying. Thus, heating 2a and 4a in the presence of AIBN (1.5 equiv.) in DCM to 80°C for 12 h, gave 5a in 13% yield. Alternatively, stirring 2a and 4a with BEt$_3$ (0.3 equiv.) under dioxygen at ambient temperature in MeCN for 12 h, gave 5a in traces (<5% yield). For a guiding reference of the latter approach, see: K. Gilmore, B. Gold, R. J. Clark, I. V. Alabugin, Aust. J. Chem. 2013, 66, 336–340.

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